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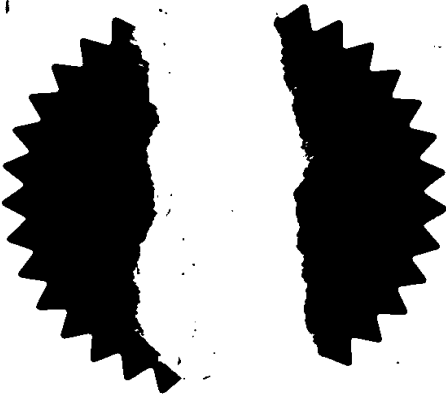
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Dated

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GB9822170.8

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of

WEST PHARMACEUTICAL SERVICES DRUG DELIVERY & CLINICAL RESEARCH  
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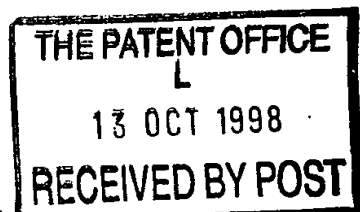
# Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1. Your reference	DANR\P19622GB		
2. Patent application number (The Patent Office will fill in this part)	13 OCT 1998	9822170.8	
3. Full name, address and postcode of the or each applicant (underline all surnames)	<p>Danbiosyst UK Ltd Albert Einstein Centre Highfields Science Park Nottingham NG7 2TN United Kingdom</p> <p>Patents ADP number (if you know it)</p> <p>If the applicant is a corporate body, give the country/state of its incorporation</p> <p>United Kingdom/Nottingham</p>		
4. Title of the invention	NOVEL FORMULATIONS OF FEXOFENADINE		
5. Name of your agent (if you have one)	<p>ERIC POTTER CLARKSON PARK VIEW HOUSE 58 THE ROPEWALK NOTTINGHAM NG1 5DD</p> <p>Patents ADP number (if you know it)</p> <p>1305010</p>		
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of filing (day / month / year)
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application		Date of filing (day / month / year)
8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer yes if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body. See note (d))	YES		



SECTION 30(1) 1/77  
53083549  
APPLICATION FILED 8-10-99

**Patents Form 1/77**

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Description 9

Claim(s) 1

Abstract 0

Drawing(s) 2 + 2 (88)

10. If you are also filing in any of the following, state how many against each item.

Priority Documents 0

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Statement of inventorship and right to grant of a patent (*Patents Form 7/77*) NO

Request for preliminary examination and search (*Patents Form 9/77*) NO

Request for substantive examination (*Patents Form 10/77*) NO

Any other documents  
(please specify)

11.

I/We request the grant of a patent on the basis of this application.

Signature

*Eric Potter Clarkson*

Date

ERIC POTTER CLARKSON

12 October 1998

12. Name and daytime telephone number of person to contact in the United Kingdom

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**Notes**

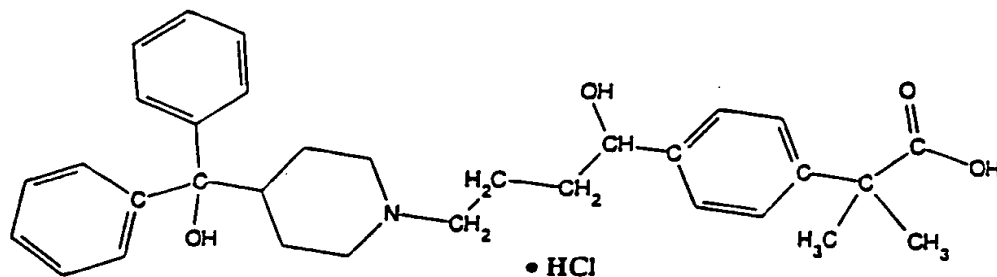
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## Novel Formulations of Fexofenadine

Fexofenadine is a recently-introduced  $H_1$ -histamine antagonist drug, indicated for relief of the symptoms of allergy. The drug is the active metabolite of another antihistamine, terfenadine. High plasma concentrations of terfenadine have been associated with rare incidences of cardiac arrhythmias and the drug is gradually being withdrawn from clinical use, with fexofenadine being promoted as a replacement.

To date only oral formulations of fexofenadine have been developed. However, nasal formulations of the drug for local treatment of allergic rhinitis would be advantageous. A particularly desirable nasal formulation for local action would be one having prolonged retention in the nasal cavity by the use of a gelling and/or bioadhesive liquid or powder formulations. A liquid formulation of fexofenadine adapted for nasal administration may also be appropriate for ophthalmic administration, although the range of excipients suitable for administration into the eye is more limited, in part because the eye has greater sensitivity than the nasal cavity.

Fexofenadine is used in the form of the hydrochloride salt (MW 538). The compound shows highest solubility between pH 2 and 3 and above pH 9. Between pH 4 and 9, the solubility of the anhydrous form is low, around 0.2-0.5 mg/ml.



*Fexofenadine hydrochloride*

The major challenge to the development of a nasal or ophthalmic formulation of fexofenadine hydrochloride is the limited solubility of the drug. A nasal dose for fexofenadine has not been established. However, based on a daily oral dose of 120 mg and the nasal/oral dose ratio for other antihistamines, a nasal fexofenadine dose in the range 1-5 mg/nostril can be assumed. Therefore, for a liquid formulation, with a 0.1 ml dose volume, a concentration of 10-50 mg/ml fexofenadine would be required.

Fexofenadine shows the highest water solubility between pH 2 and 3 and above pH 9. However for use in the nasal cavity and the eye a pH in the range 4-8 should be chosen if

possible to prevent possible irritation. The buffer capacity of the formulation is another relevant factor. A low buffer capacity is advantageous.

We have found surprisingly that the solubility of fexofenadine in water can be increased using pharmaceutical excipients in the form of cyclodextrins and in particular hydroxy propyl- $\beta$ -Cyclodextrin (HP- $\beta$ -CD)

According to the present invention there is provided a composition comprising fexofenidine or a pharmaceutically acceptable salt thereof and a pharmaceutical excipient that increases the solubility of the fexofenadine or salt in water.

Concentrations of fexofenadine can be from 100  $\mu\text{g/ml}$  to 100  $\text{mg/ml}$ . A preferred concentration range is 1-75  $\text{mg/ml}$  and a specially preferred concentration range is 10-50  $\text{mg/ml}$ . The salt forms of fexofenadine can include hydrochloride, hydrobromide, acetate, mesylate, sulphate. The hydrochloride salt is especially preferred. The base can also be used.

A gelling system containing fexofenadine hydrochloride, HP- $\beta$ -CD and pectin has also been produced to provide controlled release of fexofenadine hydrochloride in the nasal cavity. The release/diffusion rate of fexofenadine hydrochloride from the formulation was significantly reduced by the presence of pectin. A liquid gelling formulation for controlled release of drug in the nasal cavity based on pectins with low degree of esterification is the subject of a co-pending patent application (PCT/GB98/01147).

Pectin can form gels in the presence of divalent ions such as calcium. The interaction of pectin with simulated nasal electrolyte solution can form a very strong gel which may prolong the contact time of the formulation in the nasal cavity either through bioadhesive interactions and/or increase in viscosity. Pectins with a low degree of esterification can be obtained from Copenhagen Pectin A/S as the commercial material known as Slendid Type 100 and Slendid Type 110. These pectins have been extracted from citrus peel and standardised by the addition of sucrose. The degree of esterification was less than 50% for both pectins and of the order of 10% for type 100 and 35% for type 110. Further materials include GENU pectin types LM1912CS and Pomosin pectin types LM12CG and LM18CG.

By low degree of esterification we mean less than 50% and more preferably less than 35%.

The formulation may be prepared by dissolving pectin in water together with simple monovalent electrolytes eg. NaCl so as to provide isotonicity, or agents such as glycerol and

low concentrations of preservative material, eg. sodium metabisulphate. The concentration of dissolved pectin can be from 0.1% to 10% w/w but preferably from 0.5 to 5% w/w.

Cyclodextrins (CD) are industrially produced cyclic oligosaccharides which comprise glucopyranose units. The three major cyclodextrins are  $\alpha$ ,  $\beta$  and  $\gamma$  which comprise 6, 7 and 8 glucopyranose units, respectively.

Cyclodextrins for use as pharmaceutical excipients have been described in detail by Thompson, Crit. Rev. Ther. Drug Carrier Sept. 14 1 (1997). They include alpha, beta and gamma cyclodextrins as well as derivatives of beta cyclodextrins in the form of dimethyl cyclodextrin, hydroxypropyl beta cyclodextrin and Sulphobutylether cyclodextrin.

The physicochemical properties of these cyclodextrins are different - alpha cyclodextrins, beta cyclodextrins and gamma cyclodextrins have different numbers of glucose units, 6, 7, 8, respectively, as well as different water solubilities. Alpha cyclodextrin (mole. wt. 972), beta cyclodextrin (mole. wt. 1135), 2,6 dimethyl 14-beta cyclodextrin (mole wt. 1331), 2, 3, 6 trimethyl 21- beta cyclodextrin (mole. wt. 1429), hydroxypropylbetacyclodextrins (where the hydroxyl group on the hydroxypropyl substituent can exist at 1 of 3 carbons, the preferred derivative being (2HP)-B-CD, and monosubstituent sulphobutyl ether derivative of beta cyclodextrin. This last cyclodextrin has been newly introduced and is available from Cydex, Overland Park, Kansas.

The person skilled in the art would be aware of the regulatory status of these cyclodextrins and the fact that from the standpoint of toxicity they could be used for application to nasal and ophthalmic surfaces.

The concentration of the cyclodextrin used in the present invention can be from 0.5 to 20% w/v. A preferred concentration is from 1 to 10% w/v. By % w/v we mean the weight in gram of cyclodextrin that is dissolved in 100ml of water or other aqueous medium.

A typical formulation for nasal delivery could comprise 1-20mg/ml of fexofenadine hydrochloride together with 1-200mg/ml of hydroxypropylbeta cyclodextrin and 5-50mg/ml of pectin. As a compromise between solubility and acceptability for administration to mucosal surfaces a pH of 3-9 is preferred for the solution. A preferred formulation would contain 10mg/ml of fexofenadine hydrochloride, 100mg/ml of hydroxypropyl beta cyclodextrin and 10mg/ml of pectin. A pH between 4-8 is especially preferred for the solution.

The concentration of the gelling agent used in the present invention can be from 0.1 to 20% w/v. A preferred concentration is from 1 to 10% w/v. A variety of gelling materials can be used to include pectin, alginates, gellan and similar polysaccharides. A bioadhesive, retentive system based on Chitosan or Chitosan microspheres could also be used. By a bioadhesive material we mean a material that can interact with a mucosal surface such as that found in the nose or the eye. The bioadhesive effect may be achieved through the interaction of a positively charged polymer with the negative charged surface of the cells lining the nasal mucosa or the corneal cells, or by the interaction of the positively charged polymer with the negative sugar group in mucin. A gelling block copolymer such as poloxamer 427 could also be used. For this gelling polymer a concentration between 1% w/v and 30% w/v can be employed. A concentration of 5 - 20% w/v is preferred.

### **Example 1 Analytical methods for fexofenadine**

A UV method for quantifying fexofenadine hydrochloride in water at pH 4.0 was established for measuring the solubility of fexofenadine hydrochloride in water.

The solution of 1 mg/ml fexofenadine hydrochloride (Hoechst Marion Roussel) in water was prepared and the pH of the solution was adjusted to 4.0 with hydrochloric acid or sodium hydroxide. Phthalate buffer pH 4.0 was also prepared. Both solutions were scanned using a Hewlett Packard 8452A Diode Array Spectrophotometer. An absorbance wavelength of 260 nm was selected to prepare a calibration curve for fexofenadine hydrochloride in water. Phthalate buffer pH 4.0 had strong UV absorbance between 190-320 nm and was not a suitable medium for the drug.

A series solutions of fexofenadine hydrochloride prepared in water and adjusted to pH 4.0 with hydrochloric acid or sodium hydroxide at concentrations of 150, 300, 450, 600 and 750 µg/ml were assayed at 260 nm using the Hewlett Packard 8452A Diode Array Spectrophotometer. The calibration equation was as follows:  $Y = 816.284 X - 3.960$  ( $r=1.000$ , where Y is the drug concentration in mg/ml and X is the UV absorbance (linearity over 150 to 750 µg/ml).

### **Example 2**

**UV method validation for analysis of fexofenadine hydrochloride in cyclodextrin solutions at pH 4.0**

Two cyclodextrins, α-cyclodextrin (α-CD) and hydroxypropylbeta cyclodextrin (HP-β-CD), were assessed for their effect on fexofenadine hydrochloride solubility. It was intended that

the UV method would be used to measure the solubility of fexofenadine hydrochloride in cyclodextrin solutions at pH 4.0. First the UV absorbance of  $\alpha$ -CD and HP- $\beta$ -CD was investigated to establish whether they interfere with analysis of the drug.

Solutions of 100 mg/ml  $\alpha$ -CD and 100 mg/ml HP- $\beta$ -CD at pH 4.0 were prepared and UV scanned. Solutions at pH 4.0 and containing fexofenadine hydrochloride at concentrations of 150, 450 and 750  $\mu$ g/ml in water were prepared and assayed by the UV method at 260 nm.

At 260 nm, the UV absorbance of 150, 450 and 750  $\mu$ g/ml fexofenadine hydrochloride in water was 0.1900, 0.5612 and 0.9122, respectively, but the absorbance of 100 mg/ml  $\alpha$ -CD and 100 mg/ml HP- $\beta$ -CD was 0.0239 and 0.0832, respectively. The absorbance of fexofenadine hydrochloride solution was affected little by the presence of  $\alpha$ -CD and the UV method is valid to assay the concentration of the drug in  $\alpha$ -CD solutions. The 100 mg/ml HP- $\beta$ -CD caused a minor interference at 260nm. However, in an actual formulation, the UV absorbance of HP- $\beta$ -CD would be minimal compared to that of fexofenadine hydrochloride and therefore the UV method can also be used to assay the concentration of the drug in HP- $\beta$ -CD solutions.

### **Example 3 Solubility of fexofenadine hydrochloride in water and cyclodextrin solutions at pH 4.0**

#### **a) The solubility of fexofenadine hydrochloride in water at pH 4.0**

An aqueous suspension containing 10 mg/ml fexofenadine hydrochloride and at pH 4.0 was stirred for 24 hours at room temperature. The mixture was centrifuged and the supernatant was passed through a 0.45  $\mu$ m membrane filter to remove drug particles. The filtered solution was assayed by the UV method at 260 nm.

#### **b) The solubility of fexofenadine hydrochloride in cyclodextrin solutions at pH 4.0**

$\alpha$ -CD and HP- $\beta$ -CD aqueous solutions were prepared at concentrations of 10, 25, 50 and 100 mg/ml respectively. To 10 ml of each solution, 100 mg of fexofenadine hydrochloride was added, stirred and the pH of the solutions was adjusted to pH 4.0 by adding hydrochloric acid or sodium hydroxide. If the drug dissolved completely, a further 100 mg of fexofenadine hydrochloride was added and stirred until a suspension (containing

20 mg/ml fexofenadine hydrochloride) was formed at pH 4.0. The suspensions were stirred over 24 hours and centrifuged. The supernants were filtered through a 0.45  $\mu$ m membrane filter to remove drug particles, then diluted and assayed by the UV method at 260 nm.

The solubility of fexofenadine hydrochloride in water,  $\alpha$ -CD and HP- $\beta$ -CD solutions is listed in Table 1. The solubility of fexofenadine hydrochloride in water is 0.6 mg/ml. The solubility in aqueous solution was increased by both  $\alpha$ -CD and HP- $\beta$ -CD, and the enhancement of the solubility depended on the concentration of cyclodextrin in aqueous solution. The higher the concentration of cyclodextrin in solution, the higher the solubility of the drug that was obtained. HP- $\beta$ -CD improved the solubility much more than  $\alpha$ -CD. While not wishing to be bound by any theory, we believe that this increased solubility for fexofenadine in HP- $\beta$ -CD is due to the fact that fexofenadine can complex more efficiently with this cyclodextrin and perhaps fit better inside the cyclodextrin molecule. A linear relationship of fexofenadine hydrochloride solubility increasing with the concentrations of  $\alpha$ -CD and HP- $\beta$ -CD was found. It can be predicted that a higher solubility of fexofenadine hydrochloride in aqueous solution will be achieved with a higher concentration of HP- $\beta$ -CD.

**Table 1**

**The solubility of fexofenadine hydrochloride in aqueous solutions at pH 4.**

<b><u>Solution</u></b>	<b><u>The Solubility of fexofenadine hydrochloride (mg/ml)</u></b>
Water	0.6
$\alpha$ -CD	
10 mg/ml	0.6
25 mg/ml	1.2
50 mg/ml	2.7
100 mg/ml	3.3
HP- $\beta$ -CD	
10 mg/ml	1.9
25 mg/ml	3.5
50 mg/ml	8.1
100 mg/ml	13.1

The molecular weights of fexofenadine hydrochloride,  $\alpha$ -CD and HP- $\beta$ -CD are 538, 972 and 1135, respectively. At a solubility of 3.3 mg/ml fexofenadine hydrochloride in 100 mg/ml  $\alpha$ -CD aqueous solution, the weight ratio of fexofenadine hydrochloride :  $\alpha$ -CD is 1 : 30.3,

which is equal to a molar ratio of 1 : 16.8. At a solubility of 13.1 mg/ml fexofenadine hydrochloride in 100 mg/ml HP- $\beta$ -CD aqueous solution, the weight ratio of fexofenadine hydrochloride : HP- $\beta$ -CD is 1 : 7.6, which is equal to a molar ratio of 1 : 3.6.

#### **Example 4 A pectin gelling formulation for controlled release of fexofenadine hydrochloride**

The feasibility of producing a gelling formulation for controlled release of fexofenadine hydrochloride was investigated.

**Formulation 1: 10 mg/ml fexofenadine + 100 mg/ml HP- $\beta$ -CD**

2 g of HP- $\beta$ -CD was dissolved in 18-19 ml of water in a 20 ml volumetric flask. 200 mg of fexofenadine hydrochloride was added to the solution and stirred until the drug had dissolved. The pH of the solution was adjusted to 4.0 by the addition of hydrochloric acid or sodium hydroxide, then the solution was made up to volume with water.

**Formulation 2: 10 mg/ml fexofenadine + 100 mg/ml HP- $\beta$ -CD + 10 mg/ml pectin**

50 mg of pectin was dissolved in 5 ml of Formulation 1 in a 5 ml volumetric flask.

**Preparation of simulated nasal electrolyte solution**

8.77 g of sodium chloride, 2.98 g of potassium chloride and 0.59 g of calcium chloride dihydrate were dissolved in 1 litre of water in a 1 litre volumetric flask

**Release/diffusion testing**

A Franz diffusion cell apparatus was set up in a closed loop arrangement and parameters were listed as follows. Figure one shows a diagram of this system together with a diagram of the Franz Diffusion cell. The diagram of the diffusion cell shows the sample compartment the membrane that supports the formulation. The receptor compartment with stirrer where eluant can be circulated via a peristaltic pump to a cuvette in a UV spectrophotometer.

Medium:	Simulated nasal electrolyte solution
Medium temperature:	37°C
Membrane:	Cellulose nitrate, 0.45 $\mu$ m pore size
Volume of the closed loop arrangement	8.8 ml

Stirring speed of a magnetic stirrer:	4
Peristaltic pump flow rate:	1 (The Cole-Parmer Masterflex peristaltic pump, Model 7518-60, fitted with Masterflex 14 silicone tubing)
Sample volume:	0.4 ml (contained 4 mg of fexofenadine hydrochloride, the maximum concentration of the drug in medium will be around 450 µg/ml)
Drug analysis:	UV at 260 nm

Formulation 2 interacted with simulated nasal electrolyte solution and formed a strong gel when it was applied on the membrane of the diffusion apparatus. Figure 2 shows the cumulative release/diffusion of fexofenadine hydrochloride from two formulations, HP- $\beta$ -CD and pectin/HP- $\beta$ -CD, into simulated nasal electrolyte solution. The maximum UV absorbance of Formulation 1 (control) reached during the diffusion experiment represented 100% drug release and was used to calculate the percentage of release at each selected time point. The release/diffusion rate of fexofenadine hydrochloride from pectin/HP- $\beta$ -CD solution was significantly slower than from the HP- $\beta$ -CD solution. As a control solution, fexofenadine hydrochloride diffused through the membrane very rapidly with complete drug release in 10 minutes. However, after 30 minutes less than 10% of the drug had been released from the pectin formulation.

These examples show the solubility of fexofenadine hydrochloride in aqueous solution at pH 4.0 was improved significantly using cyclodextrins. The enhancement of fexofenadine hydrochloride solubility in aqueous solution depends on the concentration of cyclodextrin. HP- $\beta$ -CD increased the solubility much more than  $\alpha$ -CD. The solubilities in water, 100 mg/ml  $\alpha$ -CD and 100 mg/ml HP- $\beta$ -CD aqueous solutions at pH 4.0 were 0.6, 3.3, and 13.1 mg/ml, respectively. A pectin gelling formulation containing 10 mg/ml fexofenadine hydrochloride and 100 mg/ml HP- $\beta$ -CD showed very slow release of the drug which forms the basis of a controlled release formulation for nasal administration of fexofenadine.

It will be appreciated by the person skilled in the art that it will be possible to modify the release rate of the formulation by changing the concentration of pectin or by the use of another pharmaceutically acceptable gelling agent or biocompatible, bioadhesive agent. These include polysaccharides such as alginate, gellan and chitosan as well as a block copolymer such as the poloxamers. In addition, there are a number of other standard approaches that could be investigated for producing liquid or powder formulations which

provide controlled release of fexofenadine hydrochloride, for example, lyophilised drug/cyclodextrin/starch microsphere mixture.

The Formulation described in example 4 can be administered to the nose of a patient using a spray device and can be obtained from companies such as Valois, Pfieffer as a single dose or multiple dose system.

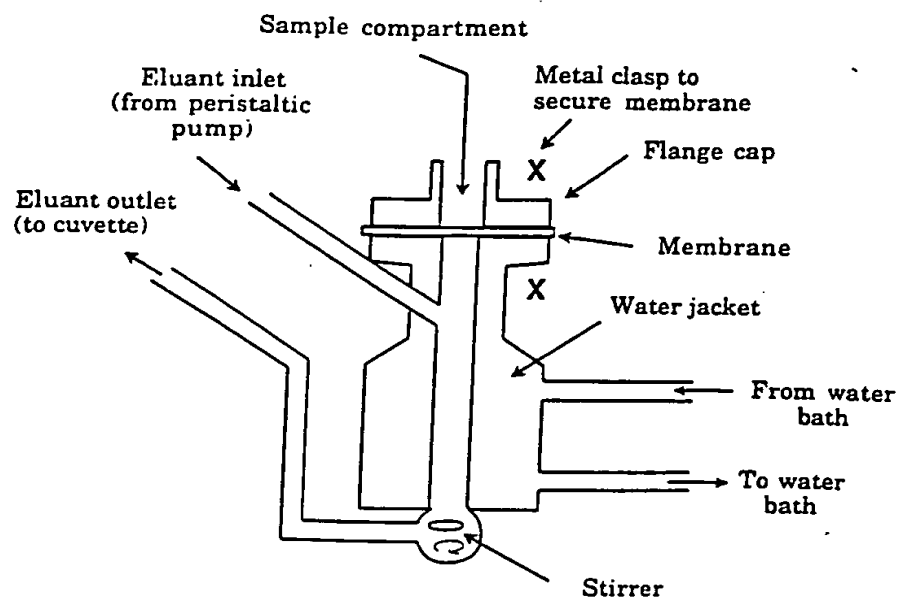
Similarly an ophthalmic Formulation can be prepared in the same manner as in Example 4 and administered to the eye using an eye dropper. For such an ophthalmic product a thickening agent can be added such as polyvinylalcohol or hypromellose.

## **Claims**

1. A composition comprising fexofenadine or a pharmaceutically acceptable salt thereof and a pharmaceutical excipient that increases the solubility of the fexofenadine or salt in water.
2. A composition comprising fexofenadine or a pharmaceutically acceptable salt thereof and a pharmaceutical excipient that increases the solubility of the fexofenadine or salt in water for the delivery of fexofenadine to the eye or nose.
3. A composition according to Claim 2 where the cyclodextrin is hydroxypropyl beta cyclodextrin.
4. A composition according to Claims 1-3 where a gelling agent or bioadhesive material is added.
5. A composition according to Claim 4 where the gelling agent or bioadhesive material is a polysaccharide.
6. A composition according to Claim 5 where the agent is selected from the group pectin, alginate, gellan, chitosan.
7. A method for the treatment of rhinitis using a composition as described in Claims 1-6.
8. The use of fexofenadine or a pharmaceutically acceptable salt thereof and a pharmaceutical excipient that increases the solubility of the fexofenadine or salt in water in the manufacture of a medicament for administration to the nose or to the eye.

1/2

## Diagram of Franz diffusion cell



## Schematic diagram of a closed loop system

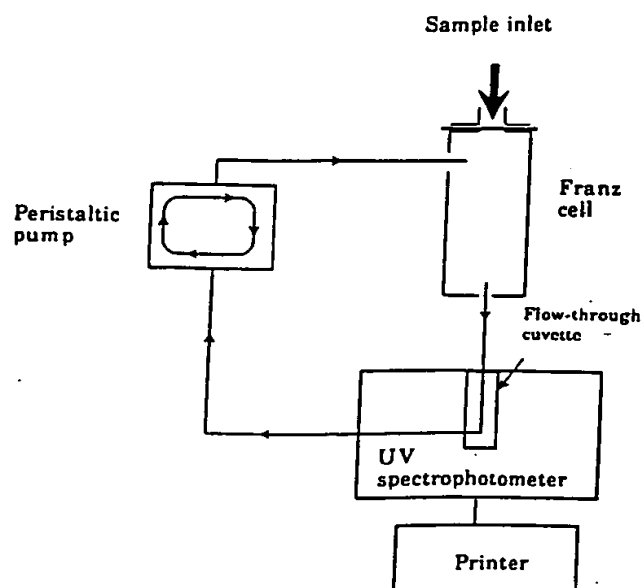


Figure 1



The cumulative release/diffusion of fexofenadine hydrochloride from HP- $\beta$ -CD and pectin/HP- $\beta$ -CD solutions to simulated nasal electrolyte solution

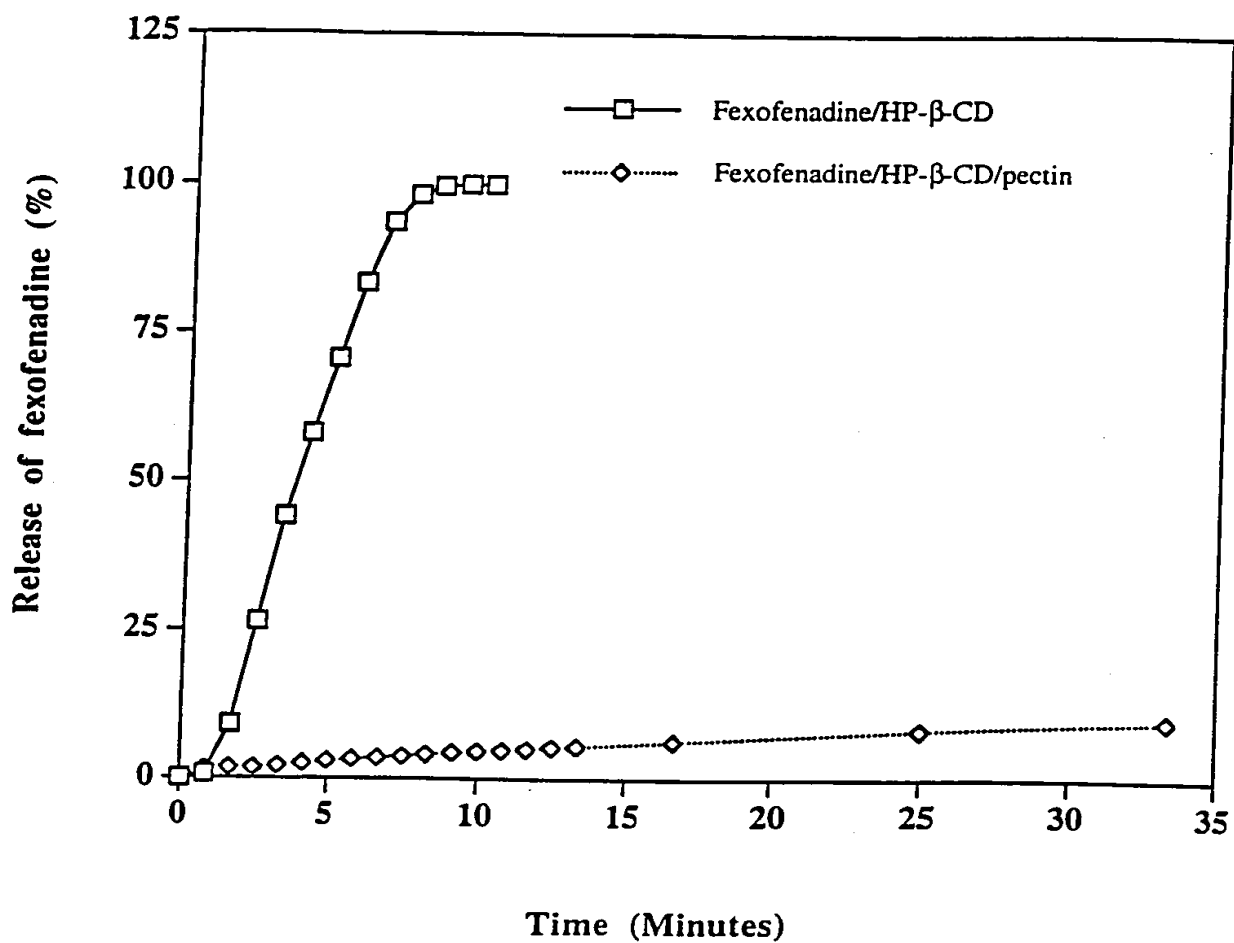


Figure 2

**AKIN, GUMP, STRAUSS, HAUER & FELD, L.L.P.**

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APPLICANT: Lisbeth ILLUM *et al.*

APPLN. NO.: 09/834,312 FILED: April 13, 2001

FOR: **NOVEL FORMULATIONS OF FEXOFENADINE**

ATTORNEY DOCKET NO.: 8567-603US (WESR/P21598US)

SHEET NO. 1 OF 1